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Molecular Dynamics Study of Amyloid Formation of Two Abl-SH3 Domain Peptides

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Two and ten antiparalel strand β-sheets built from DLSFMKG (MK) and DLSFKKGE (KK) peptides, were imersed in periodic water boxes and subjected to molecular dynamics simulations (MD) at 30K, 170K/190K - for two and ten strand β-sheets respectively, and to 300 K. MD simulations showed that 2xMK β-sheet is more stable than 2xKK β-sheet, and 10xMK β-sheet is more stable then 10xKK β-sheet, suggesting that MK systems is fibril creating and the KK systems is not.

1 Introduction

Amyloid formation and deposit is connected with Alzheimer's disease, Parkinson's disease, and Finnish familial amyloidosis. After protein misfolding short peptide sequences act as "hot spots" providing the driving force for protein aggregation in amyloid fibrils.

2 Results and Discussion

Previously we have characterized in detail one of these "hot spots" in the diverging turn of PI3-SH3 domain, one of the most extensively studied amyloidogenic proteins not related to a disease[1,2]. Based on an homology search we have identified an aggregation prone region in the same structural element of the related Abl-SH3 domain of Drosophila (DLSFMKGE) whereas the human homologous region (DLSFKKGE) is predicted to be less amyloidogenic. The possible reason for the difference of amyloid formation propensities of the two peptides was investigated by molecular dynamics (MD) of β-sheet structures. The antiparallel alanine β-sheets consisting of two and ten strands were constructed, minimized, and mutated to the sequences DLSFMKGE and DLSFKKGE. All four systems: 1) DLSFMKGE - two strands(2xMK) (fig 1 a-f), 2) DLSFKKGE - two strands (2xKK) (fig 1 g-k), 3) DLSFMKGE - ten strands (10xMK) (fig2 a-d), 4) DLSFKKGE - ten strands (10xKK) (fig 2 e-h), were surrounded by 10 Ålayer of water molecules over the solute and subjected to MD, Amber 8.0 force field, NTP protocol. The MD runs were started at the temperature of 10 K and the temperature was elevated stepwise by 10 degrees till 300 K. Longer MD runs were done at 30 K (78 ns), 170 K (140 ns) and 300

K for the two strand systems, and at 30 K (47 ns), 190 K (55 ns) and 300 K for the ten strand systems. The results (fig 2) show considerably higher hydrogen bond percentage for DLSFMKGE than that one for DLSFKKGE during the course of the simulation, thus suggesting that DLSFMKGE is a potential fibril- maker, but DLSFKKGE is not. Two strand β-sheet systems were stable until 170 K (fig 1). The ten strand β-sheets appears to be clearly more stable (fig 2). The fact that with the course of the simulation a β-sheet partly or completely melts at higher temperatures suggests, the need for a complex of several face to face oriented β-sheets to provide stability to the amyloid fibril.

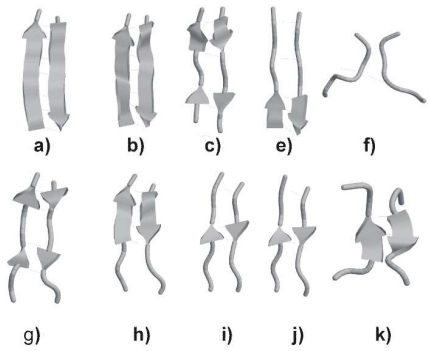

Figure 1. MD snapshots of DLSFMKGE two strand system : a) at 30K, 23159 ps, b) at 170K, 42359 ps, c) at 170 K, 91467 ps, e) at 170 K, 99126 ps, f) at 300 K, 64231 ps; MD snapshots of DLSFKKGE two strand system: g) at 30K, 19941 ps, h) at 170K, 42880 ps, i) at 170K, 92658 ps , j) at 170K, 98969 ps, k) at 300K, 94276 ps.

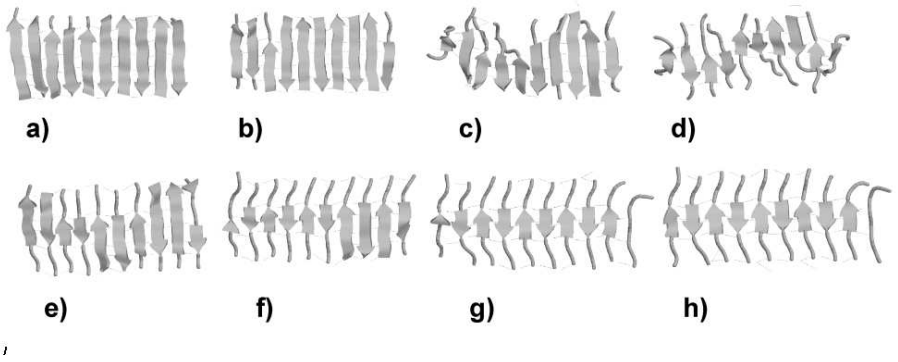

Figure 2. MD snapshots of DLSFMKGE ten strand system: a) at 30 K, 15343 ps, b) at 190 K, 58023 ps, c) at 300K, 58489 ps, d) at 300 K, 64419 ps; MD snapshots of DLSFKKGE ten strand system: e) at 30 K, 15950 ps, f) at 190K, 58588 ps, g) at 300 K, 58466 ps, h) at 300 K, 64038 ps.

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